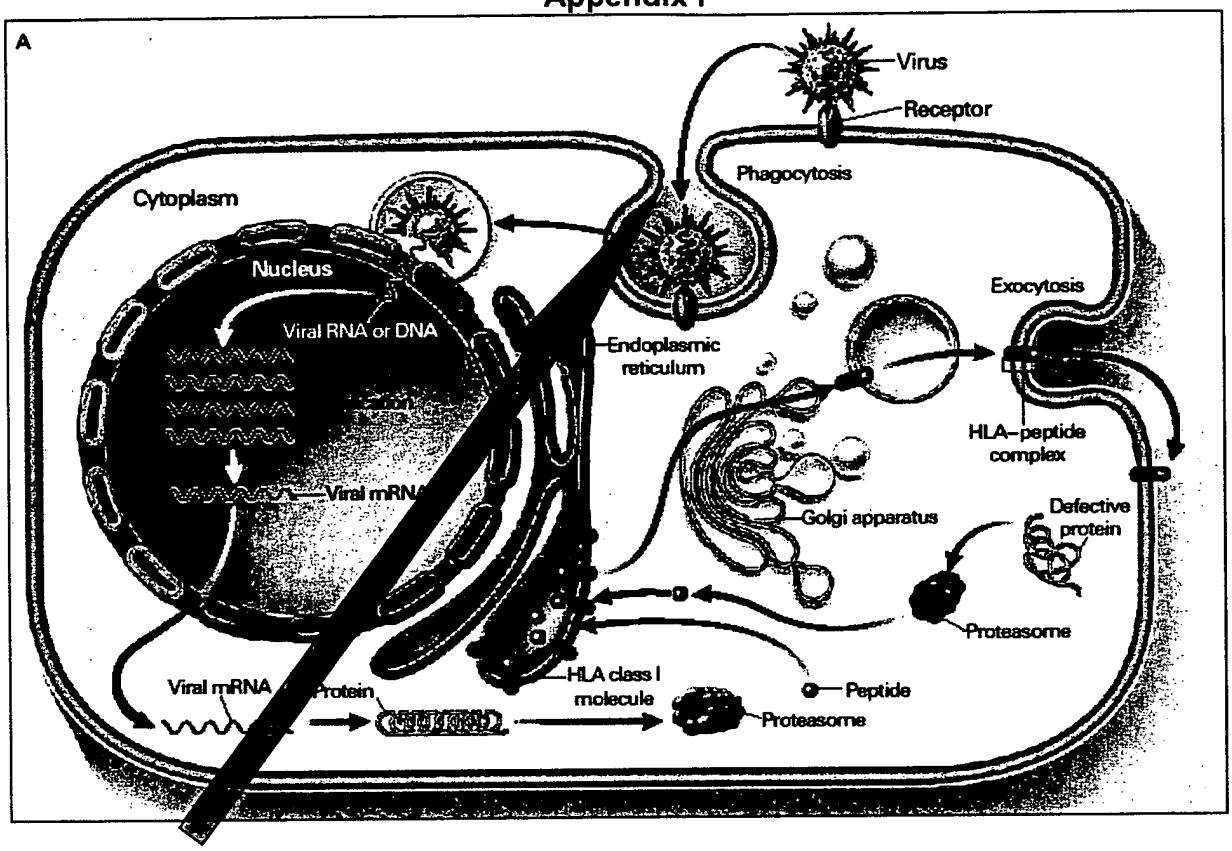
Appendix I



Figures A & B. Pathways A and B both contribute a diverse array of danger signals, pathogen associated molecular patterns and costimulatory signals during the entry/uptake phase. Conventional adjuvants (& tucaresol) are effective.

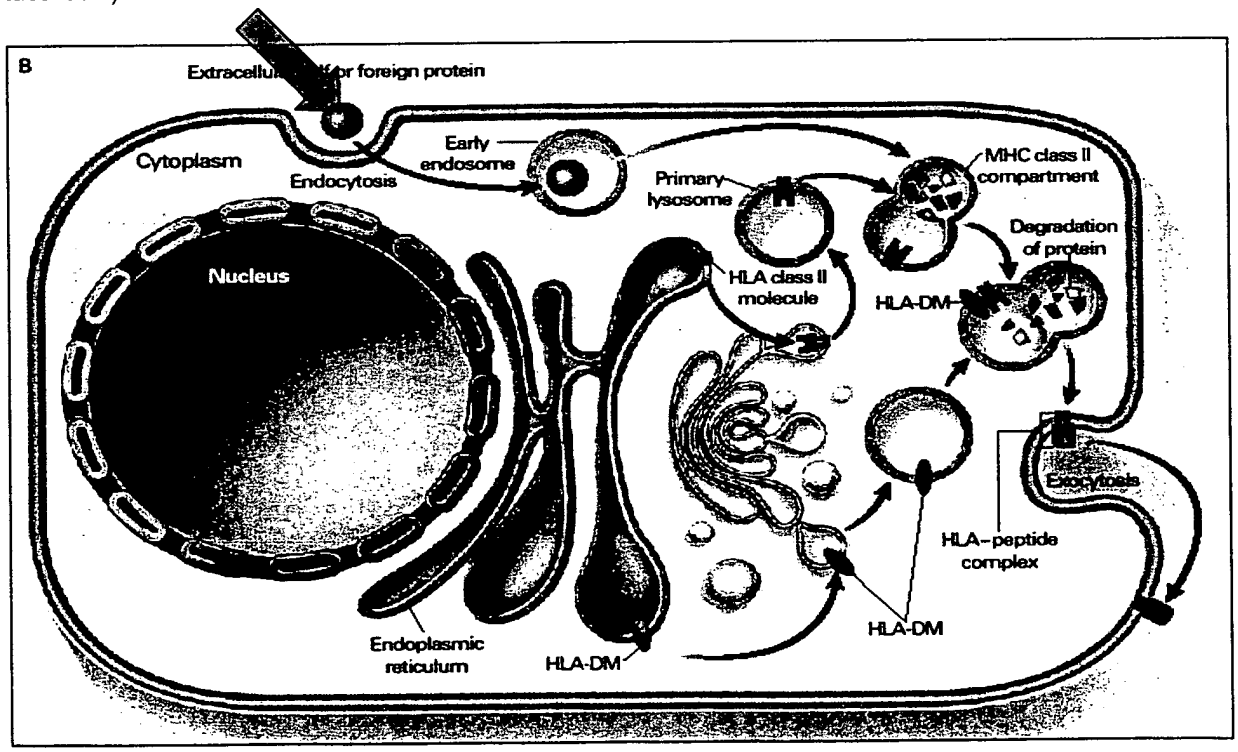


Figure C. Delivery of antigens as DNA provides no danger signals, no pathogen associated molecular patterns, and no modulation of the spectrum of costimulatory signals. Conventional adjuvants are ineffective. Tucaresol is effective.

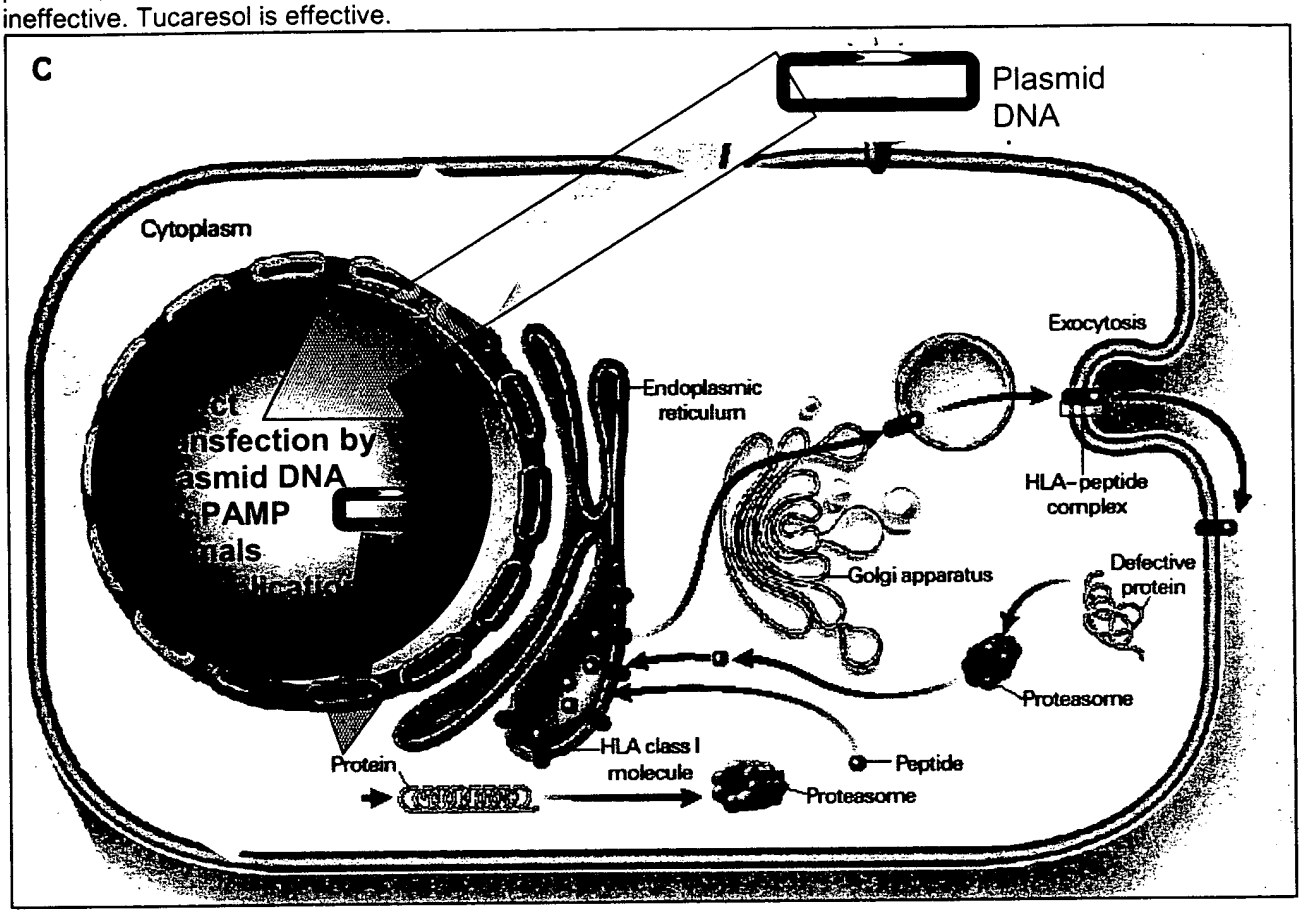


Figure D. Induction of immune responses requires two signals. Signal 1, ligation of the T-cell receptor by antigen is the same for natural infections, conventional vaccines and DNA vaccines. Signal 2 depends on events triggered by the entry/uptake of antigens in APC. Natural infections and conventional vaccination provide a number of danger/PAMP- associated signals (e.g. through toll-like receptors) during the entry uptake phase in APC. In contrast DNA vaccination does not provide these signals. Adjuvants work through the costimulatory pathways. Conventional and DNA vaccines are therefore fundamentally different with regard to adjuvant needs.